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Pulse pressure as a haemodynamic variable in systolic heart failure

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CHAPTER 3

A low pulse pressure is an independent predictor of mortality and morbidity in non ischaemic, but not in ischaemic advanced heart failure patients.

Colin J Petrie, Adriaan A Voors and Dirk J van Veldhuisen.

Int J Cardiol. 2009;131:336-44.

ABSTRACT

Background In patients with atherosclerotic disease, a high pulse pressure is an important predictor of cardiovascular events. However, in patients with chronic heart failure (CHF) a low pulse pressure is related to worse outcome, although no distinction was made between ischaemic and non ischaemic heart failure. We therefore aimed to compare the prognostic value of pulse pressure (PP) between those with ischaemic and non ischaemic advanced heart failure.

Method and Results Pulse pressure was analysed for its effect on mortality, adjusting for other modifiers of risk, using Cox proportional hazards regression analysis of data collected from 1901 patients with NYHA class III or IV heart failure (mean age 65 years, mean ejection fraction 26%). In ischaemic heart failure (n = 1118), low mean arterial pressure (MAP) was an independent predictor of overall mortality (Hazard Ratio (HR) 0.88 per 10 mmHg; p = 0.04), while pulse pressure was not. In contrast, in non ischaemic heart failure (n = 783), a low pulse pressure was an independent predictor of overall mortality (HR 0.84 per 10 mmHg; p = 0.036), while mean arterial pressure was not. In addition, higher NYHA class and lower pulse pressure (HR 0.87 per 10 mmHg; p = 0.002) were the only independent predictors for first heart failure hospitalisation in both ischaemic and non ischaemic patients.

Conclusion Low pulse pressure is a readily obtainable risk marker of death in advanced non ischaemic heart failure. Mean arterial pressure remains an important component of blood pressure in predicting mortality, especially in those with heart failure of an ischaemic aetiology. It is postulated that pulse pressure may reflect a deleterious haemodynamic state, in non-atherosclerotic heart failure patients.

INTRODUCTION

An *elevated* pulse pressure has been found to independently predict adverse cardiovascular events in normotensive, hypertensive, post myocardial left ventricular dysfunction and mild chronic heart failure patients.¹⁻⁸ Recently, we demonstrated that *lower* pulse pressure predicted adverse outcome in advanced chronic heart failure patients.⁹ Elevated pulse pressure seems to reflect arterial stiffness and atherosclerosis, while a lower pulse pressure might be more closely related to impaired haemodynamics and reduced cardiac output. In ischaemic heart failure patients, pulse pressure is a reflection of the atherosclerotic burden on the one hand (high pulse pressure), and left ventricular dysfunction on the other hand (low pulse pressure). Both entities may counteract each other. In contrast, we speculated that in non ischaemic chronic heart failure patients, pulse pressure may be more closely related to stroke volume. We therefore aimed to compare the prognostic importance of pulse pressure in patients with ischaemic heart failure compared to those with non ischaemic heart failure.

METHODS

Patients

All patients of the present study had been part of PRIME-II study. Blood pressure (BP) was measured at the randomisation visit, as per the usual practice of the participating centres. Details of the inclusion and exclusion criteria have been previously published.¹⁰ In brief, 1906 patients with advanced chronic heart failure (NYHA functional class III-IV) were randomised to ibopamine, an oral dopamine agonist, or placebo. All subjects had to have symptoms of heart failure at rest despite optimal therapy, within the 2 months before randomisation or have been recently admitted to hospital with worsening heart failure. Hospitalised patients were excluded, thus the study population was those with advanced but stable chronic heart failure. Complete blood pressure measurements were available in 1901 patients and were used for this analysis. Exclusion criteria were obstructive valve disease, obstructive or restrictive cardiomyopathy, any potentially transient cause of heart failure (e.g. acute myocarditis), uncontrolled arrhythmia (this does not include ectopy only) and a myocardial infarction during the previous 3 months. Patients with "non ischaemic heart failure" (n=783) were classified according to the most likely aetiology as follows: those with a primary dilated cardiomyopathy (n=599), primary valvular heart disease (n=94), hypertension (n=80) and "other" cause of heart failure (n=10) respectively. Ischaemic heart failure (n= 1118) was defined as those with a history of myocardial infarction (n=976) and those with a history of "ischaemic heart disease". The primary endpoint of the study was all cause mortality. Patients were aged

18-80 years, and already received optimal medical treatment with angiotensin converting enzyme (ACE) inhibitors (if tolerated) and diuretics.

Statistical analysis

Baseline characteristics of different patient categories were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. Values were expressed as mean \pm SD for continuous variables and percentages for dichotomous variables. Quartiles of pulse pressure and mean arterial pressure were chosen to try and split the patients in to roughly four even groups. The effects of pulse pressure (systolic minus diastolic blood pressure) was assessed in a Cox regression model that adjusted for mean arterial pressure ($1/3 \times$ systolic blood pressure + $2/3 \times$ diastolic blood pressure) to evaluate the relative effects on cardiovascular events of both mean arterial and pulse pressure. Established predictors of outcome in chronic heart failure¹¹⁻¹² were included in the multivariable models. These included age, gender, left ventricular ejection fraction, use of β -blockers, ACE inhibitors, diabetes mellitus, New York Heart Association (NYHA) class, baseline heart rate, weight, treatment group assignment, estimated glomerular filtration rate (GFR) (Cockcroft-Gault GFR (ml/min) = $((140 - \text{age in years}) \times (\text{body weight in kg}) / (72 \times \text{serum creatinine in mg/dl}))$), mean arterial pressure and pulse pressure. A p-value of < 0.05 was considered as statistically significant, and all tests were 2-sided. SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Overall, the mean age of enrolled subjects was 65 years, 80.5% were male and the mean ejection fraction was 26%. NYHA class III heart failure was present in 60% of the patients, 32% were in NYHA class III/IV and the remaining 8% were in NYHA class IV at trial enrolment. The aetiology of chronic heart failure was thought to be ischaemic in 59% and non ischaemic in 41%. Just over half had a prior history of myocardial infarction (53.8%) and about one third (31.5%) had a primary dilated cardiomyopathy (DCM). During a median follow up of 327 days there were 424 (22.3%) deaths and 526 patients (27.7%) experienced at least one hospitalisation for worsening heart failure. There were 144 (18.4%) deaths in the non ischaemic heart failure group compared with 280 (25%) deaths in those with ischaemic heart failure ($p < 0.001$). There were 212 (27.1%) first admissions for worsening heart failure in those with non ischaemic heart failure compared with 314 (28.1%) in those with ischaemic heart failure (NS).

Tables 1 shows the patient characteristics when groups are split according to quartiles of mean arterial blood pressure. As one moved from a higher to lower mean arterial blood pressure quartile, several significant trends were observed. Patients in the lower mean arterial blood pressure quartiles had a higher mean NYHA functional class, lower eGFR, lower left ventricular ejection fraction, lower weight and less diabetes (Table 1).

Table 2 shows the patient characteristics when groups are split according to quartiles of pulse pressure. As one moved from a higher to a lower pulse pressure quartile, different significant trends were observed. Patients in the lower pulse pressure quartiles were younger, more often male, had higher heart rates, higher NYHA functional class, higher

Table 1. Patient characteristics according to baseline quartile of mean arterial pressure

Quartile of MAP (mmHg)	First	Second	Third	Fourth	p Value
MAP Pressure range	>100	91-100	83-90	≤ 82	-
Number (%)	344 (18)	573 (30)	505 (27)	479 (25)	-
MAP (SD)	110 (7)	96 (3)	87 (3)	75 (6)	-
SBP (SD)	149 (14)	129 (10)	116 (9)	100 (9)	-
DBP (SD)	90 (8)	80 (5)	72 (5)	62 (6)	-
Pulse Pressure (SD)	59 (16)	49 (14)	43 (12)	38 (10)	-
Age (SD) (yr)	65 (10)	65 (9)	65 (9)	64 (10)	0.791
Gender (% female)	23	20	19	17	0.123
Heart Rate (SD)	83 (15)	81 (14)	79 (14)	82 (16)	0.001
NYHA class III (%)	64	70	59	46	< 0.001
NYHA class III/IV (%)	30	25	33	40	< 0.001
NYHA class IV (%)	6	5	8	14	< 0.001
GFRe (SD) (ml/min)	67 (29)	64 (26)	61 (25)	60 (25)	< 0.001
Ejection fraction (SD)	28 (10)	26 (8)	26 (8)	25 (10)	< 0.001
Weight (Kg)	79 (15)	76 (14)	74 (13)	72 (13)	< 0.001
History of diabetes (%)	26	20	18	21	0.036
Ischaemic aetiology	54	58	60	62	0.108
Previous MI (%)	49	52	55	58	0.098
Aetiology DCM (%)	33	32	32	30	0.808
ACE inhibitor use (%)	91	91	91	93	0.649
Ibopamine use (%)	50	51	51	48	0.709
β-blocker use (%)	7	7	6	5	0.490
No. Deaths (%)	60 (3.2)	110 (5.8)	114 (6%)	140 (7.4)	<0.001
Hosp. for CHF (%)	72 (3.8)	131 (6.9)	140 (7.4)	183 (9.6)	<0.001

Key MAP- mean arterial pressure NYHA –New York heart Association
 SBP-systolic blood pressure GFRe- estimated glomerular filtration rate
 DBP- diastolic blood pressure MI- myocardial infarction
 DCM- dilated cardiomyopathy ACE- angiotensin converting enzyme

Table 2. Patient characteristics according to baseline quartile of pulse pressure

Quartile of Pulse Pressure	First	Second	Third	Fourth	p Value
Pulse Pressure range	>55	>46-55	35-45	<35	-
Number (%)	506 (26)	496 (26)	430 (23)	469 (25)	
Pulse Pressure (SD)	66 (11)	49 (2)	40 (1)	30 (5)	-
SBP (SD)	144 (16)	125 (11)	112 (10)	103 (11)	-
DBP (SD)	78 (12)	76 (11)	72 (10)	74 (11)	-
MAP (SD)	100 (12)	92 (11)	85 (10)	84 (11)	-
Age (SD) (yr)	67 (8)	66 (9)	64 (10)	61 (10)	< 0.001
Gender (% female)	25	21	17	15	< 0.001
Heart Rate (SD)	80 (15)	80 (15)	80 (14)	84 (15)	< 0.001
NYHA class III (%)	65	60	59	55	0.016
NYHA class III/IV (%)	29	33	32	34	0.276
NYHA class IV (%)	7	7	9	11	0.05
GFR _e (SD) (ml/min)	61 (26)	60 (24)	65 (28)	66 (27)	0.001
Ejection fraction (SD)	29 (10)	26 (8)	26 (9)	24 (9)	< 0.001
Weight (Kg)	76 (14)	74 (13)	75 (14)	75 (14)	0.361
History of diabetes (%)	28	19	20	16	< 0.001
Ischaemic aetiology	61	60	57	57	0.457
Previous MI (%)	55	56	52	52	0.485
Aetiology DCM (%)	27	29	34	37	0.001
ACE inhibitor use (%)	88	93	93	93	0.016
Ibopamine use (%)	47	54	48	51	0.164
β-blocker use (%)	7	5	8	5	0.170
No. Deaths (%)	96 (5)	92 (4.8)	96 (5)	140 (7.4)	<0.001
Hosp. for CHF (%)	119 (6.3)	121 (6.4)	117 (6.2)	169 (8.9)	<0.001
Key MAP- mean arterial pressure NYHA –New York heart Association					
SBP-systolic blood pressure GFR _e - estimated glomerular filtration rate					
DBP- diastolic blood pressure MI- myocardial infarction					
DCM- dilated cardiomyopathy ACE- angiotensin converting enzyme					

eGFR, lower left ventricular ejection fraction, less diabetes, more dilated cardiomyopathy, and more ACE-inhibitor use (Table 2).

Table 3 illustrates the baseline demographic and clinical characteristics in those with ischaemic and non ischaemic heart failure. Those with non ischaemic heart failure are younger, more likely to be female, with higher baseline heart rates and more preserved renal function. They had similar systolic blood pressures but marginally higher diastolic blood pressures, similar ejection fractions and were well matched with regard to ACE inhibitor and diuretic use. Not surprisingly in the non ischaemic group there were fewer diabetics and more with atrial fibrillation and left ventricular hypertrophy on their base-

Table 3. Baseline characteristics of patients according to aetiology of heart failure

	Ischaemic HF (n 1118)	Non ischaemic HF (n 983)	P
Age	66 (8)	62 (10)	< 0.001
Sex (% male)	83.7	75.7	< 0.001
SBP	121 (19)	122 (20)	0.252
DBP	74 (10)	77 (11)	< 0.001
MAP	90 (12)	92 (13)	0.002
PP	47 (14)	45 (15)	0.086
Heart Rate (bpm)	80 (14)	83 (16)	< 0.001
Weight (Kg)	74 (12)	76 (15)	0.02
Creatinine (μmol/l)	125 (45)	113 (44)	< 0.001
Ibopamine use (%)	50	50	0.51
Diuretic use (%)	99	98	0.14
ACE I use (%)	91	91	0.18
β-blocker use (%)	7.2	5	0.043
Diabetes	257 (23)	137 (17)	0.002
NYHA III	666 (60)	470 (60)	0.440
NYHA III/IV	359 (32)	245 (31)	0.372
NYHA IV	93 (8)	68 (9)	0.420
Ejection fraction (%)	26 (9)	26 (9)	0.870
Serum Sodium (meq/L)	138 (4)	138 (4)	0.235
Normal ECG	24 (2)	48 (6)	< 0.001
Sinus Rhythm	854 (76)	466 (60)	< 0.001
Atrial Fibrillation	189 (17)	260 (33)	< 0.001
IVCD on ECG	516 (46)	420 (54)	< 0.001
LVH on ECG	111 (10)	206 (23)	< 0.001
Deaths (%)	280 (66)	144 (34)	< 0.001
CHF hospitalisation (%)	314 (60)	212 (40)	0.333

Data presented as mean (with SD in brackets) or numbers (with % in brackets) unless stated otherwise.

Key PP- pulse pressure
 MAP- mean arterial pressure
 b.p.m- beats per minute
 ACE I- angiotensin converting enzyme inhibitor
 NYHA –New York heart Association
 ECG- Electrocardiogram
 IVCD- Intraventricular Conduction Defect
 LVH- Left Ventricular Hypertrophy
 CHF- Chronic Heart Failure

line electrocardiograms. Whereas systolic blood pressure is often coupled with “pump” function and ejection fraction, diastolic blood pressure may be more indicative of the peripheral vasculature, and related to peripheral perfusion. We found no difference in systolic blood pressures in those with ischaemic and non ischaemic heart failure, but in-

terestingly an increased diastolic blood pressure in the non ischaemic group. Although only a very modest increase, this was statistically significant ($p < 0.01$). In our cohort, low systolic blood pressure was positively correlated with a lower ejection fraction, although only weakly ($r = 0.173$, $p < 0.01$) but ejection fraction itself is a relatively poor indicator of outcome in this population, and although significant in isolation, it is non significant in a multivariable analysis, suggesting other factors are more important (or incremental) in determining outcome. In ischaemic heart failure, ejection fraction and pulse pressure were poorly correlated ($r = 0.126$) but interestingly in those with non ischaemic heart failure, ejection fraction and pulse pressure were more strongly related ($r = 0.276$, $p < 0.01$).

Multivariable analysis

Tables 4, 5 and 6 show the results of Cox-regression multivariable analysis with all cause mortality and hospital admission for worsening heart failure as end points. Figures 1 and 2 show Kaplan-Meier survival plots for those with ischaemic and non ischaemic heart failure, across quartiles of pulse pressure. Figures 3 and 4 illustrate Kaplan-Meier survival

Table 4. Cox proportional hazards model of ischaemic heart failure and all cause mortality

N=1118 280 (25%) deaths	Hazard Ratio	95%CI	P value
PP	0.949 (per 10 mmHg increase)	0.848-1.063	0.368
MAP	0.880 (per 10 mmHg increase)	0.778-0.995	0.042
Ejection fraction	0.990 (per % increase)	0.976-1.003	0.137
Heart rate	1.007 (per b.p.m increase)	0.999-1.016	0.102
Estimated GFR	0.985 (per ml/min/1.73m ²)	0.977-0.994	0.001
Weight	0.996 (per Kg increase)	0.983-1.010	0.586
Ibopamine use	1.352	1.049-1.742	0.020
ACE I use	0.510	0.356-0.731	< 0.001
β-blocker use	0.343	0.141-0.836	0.019
NYHA class			< 0.001
NYHA class III/IV	1.290	0.981-1.695	0.068
NYHA class IV	2.355	1.602-3.462	< 0.001
Diabetes	1.596	1.206-2.112	0.001
Age	0.999	0.979-1.020	0.950
Male gender	1.306	0.901-1.894	0.158

Key

- PP- pulse pressure
- MAP- mean arterial pressure
- b.p.m- beats per minute
- GFR- glomerular filtration rate
- ACE I- angiotensin converting enzyme inhibitor
- NYHA –New York heart Association

Table 5. Cox proportional hazards model of non ischaemic heart failure and all cause mortality

N=783 144 (18.4%) deaths	Hazard Ratio	95%CI	P value
PP	0.840 (per 10 mmHg increase)	0.714-0.988	0.036
MAP	0.980 (per 10 mmHg increase)	0.829-1.158	0.808
Ejection fraction	0.986 (per % increase)	0.965-1.007	0.197
Heart rate	1.014 (per b.p.m increase)	1.003-1.026	0.016
Estimated GFR	0.999 (per ml/min/1.73m ²)	0.987-1.011	0.886
Weight	0.974 (per Kg increase)	0.957-0.991	0.003
Ibopamine use	1.426	0.998-2.036	0.051
ACE I use	0.314	0.185-0.534	< 0.001
β-blocker use	0.658	0.207-2.097	0.479
NYHA class			< 0.001
NYHA class III/IV	2.484	1.675-3.683	< 0.001
NYHA class IV	2.670	1.507-4.731	0.001
Diabetes	1.121	0.707-1.776	0.628
Age	1.041	1.015-1.068	0.002
Male gender	1.807	1.124-2.904	0.015

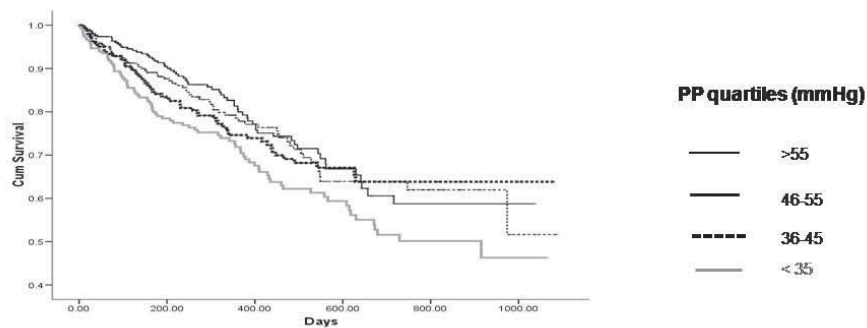
Key PP- pulse pressure
MAP- mean arterial pressure
b.p.m- beats per minute
GFR- glomerular filtration rate
ACE I- angiotensin converting enzyme inhibitor
NYHA –New York heart Association

plots for those with ischaemic and non ischaemic heart failure, across quartiles of mean arterial pressure. Overall, both mean arterial pressure and pulse pressure were independent predictors of mortality, as we demonstrated before.⁹ In addition, if proportional pulse pressure (pulse pressure divided by systolic blood pressure) was included with mean arterial pressure in the multivariable models, then both appear to be independent predictors of overall survival. The hazard ratio for all cause mortality (HR) is 0.855 per 10 mmHg increase in mean arterial pressure; 0.785-0.931; $p < 0.001$, and 0.984 per 10mmHg increase in pulse pressure (0.970-0.998; $p = 0.030$). However, in ischaemic heart failure patients, a lower mean arterial pressure was associated with increased mortality (HR 0.880 per 10 mmHg; 0.778-0.995; $p = 0.042$), while in these patients, pulse pressure was not independently associated with mortality (HR 0.949; $p = 0.368$). In contrast, in non ischaemic patients, a lower pulse pressure was associated with increased mortality (HR 0.840 per 10 mmHg; 0.714-0.988; $p = 0.036$), while in these patients, mean arterial pressure was not independently associated with mortality (HR 0.980; $p = 0.808$; tables 3, 4). In the overall study population diabetes is a significant predictor of mortality (HR 1.472; 1.163-1.863; $p = 0.001$). However, in non ischaemic heart failure, diabetes no

Table 6. Cox proportional hazards model of worsening heart failure requiring hospitalisation

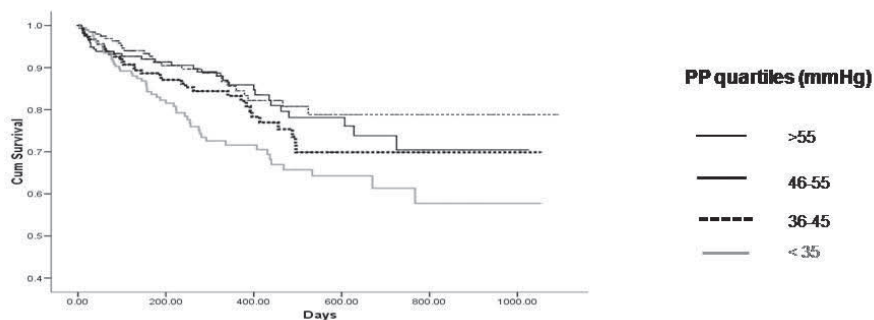
N=1901 526 (27.7%)	Hazard Ratio	95%CI	P value
PP	0.872 (per 10 mmHg increase)	0.801-0.950	0.002
MAP	0.981 (per 10 mmHg increase)	0.900-1.069	0.663
Ejection fraction	1.000 (per % increase)	0.990-1.011	0.974
Heart rate	1.002 (per b.p.m increase)	0.996-1.008	0.509
Estimated GFR	0.997 (per ml/min/1.73m ²)	0.991-1.003	0.335
Weight	0.996 (per Kg increase)	0.987-1.005	0.426
Ibopamine use	1.048	0.868-1.265	0.624
ACE I use	0.981	0.713-1.348	0.904
β-blocker use	0.896	0.498-1.611	0.714
NYHA class			< 0.001
NYHA class III/IV	1.351	1.104-1.652	0.003
NYHA class IV	1.950	1.446-2.629	<0.001
Diabetes	1.113	0.886-1.397	0.358
Age	0.999	0.985-1.013	0.871
Male gender	0.903	0.688-1.185	0.462
Key			
PP- pulse pressure			
MAP- mean arterial pressure			
b.p.m- beats per minute			
GFR- glomerular filtration rate			
ACE I- angiotensin converting enzyme inhibitor			
NYHA –New York heart Association			

longer predicted outcome. In addition, in non diabetic subjects (n = 1506; 80%), mean arterial pressure loses its robustness as a predictor of mortality (HR 0.896 per 10 mmHg; 0.800-1.004; p = 0.058) and is out played by pulse pressure (HR 0.878 per 10 mmHg; 0.787-0.980; p = 0.02). As stated previously, 526 patients (27.7%) experienced at least one hospitalisation for worsening heart failure and 10 % of the overall study population was hospitalised twice or more. NYHA class and a low pulse pressure were the only significant predictors of heart failure hospitalisation, independent of other well established prognostic variables (HR 0.872 per 10 mmHg; 0.801-0.950; p = 0.002; see table 5). The effect of pulse pressure is even more pronounced in predicting hospitalisation for worsening heart failure in non-diabetic patients (HR 0.858 per 10 mmHg; 0.765-0.963; p = 0.009) compared to those with diabetes (HR 0.879; 0.772-1.002; p = 0.054).



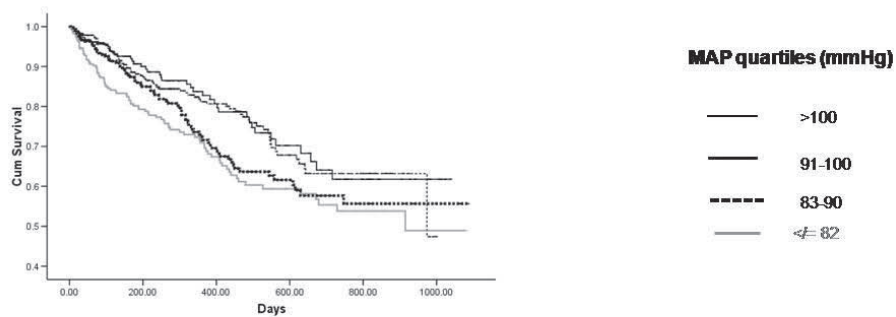
Log rank 9.58; $p=0.022$

Figure 1. Kaplan Meier survival curves by quartile of pulse pressure in ischaemic heart failure.



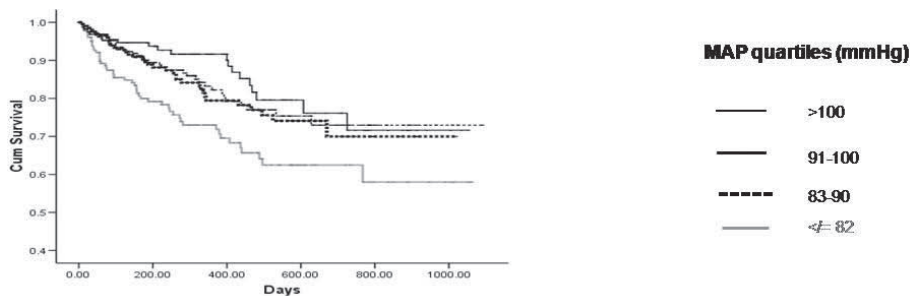
Log rank 12.11; $p=0.007$

Figure 2. Kaplan Meier survival curves by quartile of pulse pressure in non-ischaemic heart failure.



Log rank 14.70; $p=0.002$

Figure 3. Kaplan Meier survival curves by quartile of mean arterial pressure in ischaemic heart failure.



Log rank 15.04; $p=0.002$

Figure 4. Kaplan Meier survival curves by quartile of mean arterial pressure in non- ischaemic heart failure.

DISCUSSION

Recently, we demonstrated that in advanced stable chronic heart failure, a low pulse pressure is an independent predictor of mortality, and was also independently related to increased levels of natriuretic peptides⁹ which themselves confer prognostic significance.¹³ In patients who were hospitalised with decompensated heart failure a lower pulse pressure was an independent predictor of all cause mortality.¹⁴ In a large nationwide survey ($n=8660$) again a low pulse pressure was an independent predictor of mortality in congestive heart failure.¹⁵ The novel finding of the present paper is that there is a significant difference in the prospective value of pulse pressure to predict survival in ischaemic and non ischaemic heart failure.

Pulse pressure is simply the arithmetic difference between systolic and diastolic blood pressure. The circulation serves to distribute cardiac output through a series of branching networks. Wave reflection occurs throughout the arterial tree, whereby part of the forward traveling pulse wave is reflected back towards the heart, where it summates with the forward traveling wave. Therefore pulse pressure increases when arterial compliance decreases, such as in atherosclerotic vessels.¹⁶ On the other hand, pulse pressure also depends on haemodynamic factors such as stroke volume and peak aortic blood flow. In fact, in a study by Stenenson and Perloff, a low proportional pulse pressure was strongly correlated with a low cardiac index in advanced chronic heart failure ($r=0.82$; $p < 0.001$), and with stroke volume index ($r=0.78$; $p < 0.001$).¹⁷ Of note, the patients in this study were predominantly male with a dilated cardiomyopathy and were all in NYHA class IV, with a mean ejection fraction of 18%. When proportional pulse pressure was less than 25%, it had a 91% sensitivity and 83% specificity for a cardiac index of less than $2.2\text{L}/\text{min}/\text{m}^2$.¹⁷ In this same study there was a poor correlation between cardiac

index and mean arterial ($r = 0.05$) and systolic blood pressures ($r = 0.36$). In addition, Shah et al. demonstrated that pulse pressure was the only independent predictor of an impaired cardiac index ($< 2.2 \text{ L/min/m}^2$).¹⁸ Pulse pressure therefore reflects a complex interplay between stroke volume, heart rate, peak aortic blood flow, aortic distensibility and peripheral vascular tone. We postulate that “ischaemic aetiology” is a marker of generalised atherosclerosis, and those with “non ischaemic” cardiomyopathy do not have the confounding effects of atherosclerosis on pulse pressure derivation. Perhaps in those with non ischaemic cardiomyopathy (and thus without coronary artery disease; but more importantly without generalised vascular disease elsewhere), the effects of pulse pressure more closely mirror cardiac output and central haemodynamics.

This might in part explain our findings, whereby those with a non ischaemic compared to an ischaemic aetiology, pulse pressure is more powerful in predicting mortality and morbidity than mean arterial pressure. Although pulse pressure seems to be more robust in predicting outcome in the non ischaemic aetiology, we acknowledge there is still a relationship between pulse pressure and survival in those with ischaemic heart failure. This can be seen in the Kaplan Meier survival curves. This diversity was further supported by the observation that a significant correlation was found between left ventricular ejection fraction and pulse pressure only in patients with non ischaemic heart failure, but not in those with ischaemic heart failure.

In addition, lower mean arterial pressure is a robust predictor of outcome in ischaemic heart failure, itself more prevalent and with a poorer prognosis than its non ischaemic counterpart. Of course, there is co-linearity between pulse, mean and systolic pressures, and part of the association of low pulse pressure is secondary to a low systolic blood pressure. However, we chose to analyse mean arterial and pulse pressure, as from a physiological perspective these blood pressure components represent very different haemodynamic profiles (i.e steady state versus pulsatile flow respectively).

Another haemodynamic parameter of importance in determining blood pressure and survival is heart rate. Recently Aranda et al.¹⁹ reported on the prognostic power of a heart rate and blood pressure “haemodynamic profile” in identifying outcome in advanced heart failure. Those with resting heart rates $\geq 90/\text{min}$ and systolic blood pressures $< 100 \text{ mmHg}$ had the worst outcomes, when compared with heart rates < 90 and systolic blood pressure $\geq 100 \text{ mmHg}$ respectively. Heart rate and ejection fraction are positively correlated but as heart rate falls there is a rise in diastolic blood pressure. The relationship between pulse pressure and heart rate seems to be related more to changes in diastolic blood pressure, as there was no correlation with systolic blood pressure and heart rate. However in the ischaemic group, there was not even a correlation between heart rate and diastolic blood pressure ($r = 0.035$, NS) but there was in the non ischaemic group ($r = 0.205$, $p < 0.01$). In addition, an increased heart rate was only an independent predictor of survival in those with a non ischaemic aetiology.

There was marginally less β -blocker use in this group (5% in non ischaemic versus 7.2% in ischaemic) which may reflect subsequent survival and explain the differences in resting heart rates, but the overall uptake of β -blockers was very low. This is because the study started recruitment in 1992 and finished in 1995, prior to the publication of the major trials that demonstrated the benefits of β -blockers in heart failure. Naturally, this is a limitation of the present analysis. There did seem to be a beneficial effect of β -blocker use in those with ischaemic heart failure although it is likely that the overall survival benefit has been under estimated, given the relatively short duration of follow up and low usage in this study. β -blockers have negative inotropic and negative chronotropic effects, and thus may influence pulse pressure. Common wisdom may perceive β -blockers as blood pressure lowering medications, however the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) study provided an example whereby β -blocker therapy in patients with heart failure resulted in an increase in blood pressure compared with placebo and improved survival.²⁰ ACE inhibition decreases blood pressure wave reflection, reduces pulse-wave velocity and can increase arterial compliance and conduit vessel diameter. The observed reductions in mortality with ACE inhibitors were associated with only modest reductions in blood pressure and it is plausible there was an underestimate of the reduction in central aortic systolic and pulse pressures, as has been recently reported in a large hypertension trial.²¹

Since the patients from our study were randomized to ibopamine or placebo, we specifically focused on the confounding effect of ibopamine use on the present results. The effect of ibopamine on mortality and morbidity was similar between ischaemic and non ischaemic patients, between patients with higher and lower pulse pressure, and between higher and lower mean arterial pressure (data not shown). So, no confounding effect of the use of ibopamine could be demonstrated.

Our observation that in those without diabetes, pulse pressure was an independent predictor of outcome, over and above mean arterial pressure, further supports our theory relating to changes in the peripheral vasculature, as diabetes is a well established cause of peripheral and central arterial stiffness.^{22,23} Loss of arterial compliance may be both the cause and consequence of arterial disease. The most important mechanism of accelerated arterial stiffening in diabetics appears to be the reaction between glucose and the proteins of the extracellular matrix called non-enzymatic glycation, leading to the formation of advanced glycation end products (AGE's) on the extracellular matrix.^{24,25} They are the main structural alterations at the site of the large artery media and account for the arterial stiffness and increase in systolic blood pressure and pulse pressure seen in diabetics.²⁶

Similar to the current findings, we recently described that in mild chronic heart failure, renal function is a prognostic risk marker for long-term mortality in non ischaemic chronic heart failure, but *not* in patients with coronary artery disease.²⁷ This data again

suggest that atherosclerotic disease is not primarily responsible for the prognostic value of renal function. In fact renal dysfunction probably more closely reflects haemodynamic status, which is itself related to mortality. We therefore propose that haemodynamic status is probably the most important predictor of mortality and morbidity in patients with chronic heart failure, and that both lower pulse pressure and renal function closely reflect haemodynamic status. It is not surprising that more advanced NYHA class is predictive of worsening heart failure requiring hospitalization, as symptom deterioration would be rapidly detected and acted on accordingly, especially in the context of a clinical trial. However, NYHA class is a relatively crude scale, with little to discriminate between those with more advanced disease. In the overall cohort, a low pulse pressure was a significantly better haemodynamic discriminator than either ejection fraction, heart rate or mean arterial pressure, in identifying those who experience worsening heart failure requiring hospitalization.

STUDY LIMITATIONS

We extrapolated mean arterial and pulse pressure from a cuff measurement of blood pressure, and thus may not mirror central haemodynamics. "Peripheral" pulse pressure, does not represent "central" pulse pressure (that is pulse pressure in the proximal aorta) or "what the heart sees". Central pulse pressure is related to the presence and extent of coronary artery disease in men undergoing diagnostic coronary angiography²⁸ and peripheral arterial compliance is independently associated with angiographic coronary disease.²⁹ The most obvious limitation to this analysis is that it is retrospective in nature and the study was never designed to interpret outcomes in terms of aetiology of heart failure. In addition, sub group analyses should always be interpreted with caution. The increased prevalence of atrial fibrillation in the non ischaemic group may have bearing on the accuracy of baseline blood pressure measurement. However, this would happen in the "real world". The study population was recruited before the widespread use of β -blocker usage in addition to aldosterone antagonists, angiotensin receptor blockers and device therapy, which may have influences on blood pressure as well as survival. This type of analysis should be thought of as "hypothesis generating" only and prospective studies looking at both peripheral and central pulse pressures, in subjects with documented vascular disease, and those without, and correlating this with central haemodynamic measurements may help us unravel the complexity of haemodynamics in chronic heart failure.³⁰

CONCLUSION

Low pulse pressure is an independent predictor of death, in advanced chronic heart failure secondary to a non ischaemic aetiology. It appears more robust than mean arterial pressure, itself a well established marker of poor outcome in chronic heart failure. Mean arterial pressure remains an important component of blood pressure in predicting mortality in those with heart failure of an ischaemic aetiology. This remains an important observation as ischaemic heart failure is more prevalent and seems to have a worse prognosis than its non ischaemic counterpart. In addition, a low pulse pressure is a powerful predictor of hospitalisations for worsening heart failure and appears to be incremental to other well established markers of adverse outcome in this population. These findings suggest that a low pulse pressure closely reflects an impaired haemodynamic status in non atherosclerotic advanced chronic heart failure.

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